REMARKS

Applicants address the examiner's remarks in the order presented in the Office action, using the paragraph numbering from the Office action for further reference. All claim amendments are made without prejudice and do not represent an acquiescence in any ground of rejection.

STATUS OF THE CLAIMS

Claims 1-6 and 8-30 have been canceled. Claim 7 has been amended. Therefore claim 7 will be pending after entry of this amendment. Support for the claim amendments can be found in the claims as filed and throughout the specification. For example, support for step (d) in claim 7 can be found at page 20, see Table 1; at page 28, see Table 4; in the Examples beginning at page 33; and throughout the specification. All of the amendments are fully supported by the specification as filed and no new matter has been added.

Claim 7 is rejected under 35 U.S.C. §102(b) as anticipated by Condra *et al.* Claim 7 is rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement.

REJECTION UNDER 35 U.S.C. §102(B)

¶2. Claim 7 was rejected under 35 U.S.C. §102(b) as allegedly anticipated by Condra *et al.* More specifically, the examiner stated that the reference evaluated effectiveness of antiviral therapy of HIV patients with protease inhibitor Indinavir (IDV). The examiner is of the opinion that all the elements of applicants' invention with respect to the method of claim 7 are instantly disclosed by the teaching of Condra *et al.*

Although applicants do not necessarily concur, they have attempted to advance prosecution by amending claim 7 to recite that the antiviral therapy includes nucleoside reverse transcriptase inhibitors (NRTIs) which are one or more drugs of the group selected from zidovudine (ZDV), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC) and abacavir (ABC); non-nucleoside reverse transcriptase inhibitors (NNRTIs) which are one or more drugs of the group selected from nevirapine (NVP), delavirdine (DLV) and efavirenz; and protease inhibitors (PIs) which are one or more drugs of the group selected from saquinavir (SQV), ritonavir (RTV), indinavir (IDV) nelfinavir (NFV), amprenavir (APV) and ABT-378.

Claim 7 has been amended for greater clarity and consistency of claim language. More specifically, three nucleic acids enclosing mutations for NNRTIs, NRTIs *and* PIs, are evaluated for determining effectiveness of an antiviral therapy.

Accordingly, applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

¶4. Claim 7 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement because practice of the claimed invention allegedly would entail undue experimentation. Applicants respectfully traverse because there is no evidence of record so much as suggesting that those skilled in the art would be unable to practice the claimed invention.

THE NATURE OF THE INVENTION

The examiner fails to provide any evidence that the nature of applicant's invention is such that it could not be practiced by those skilled in the art.

THE STATE OF THE PRIOR ART

The examiner relies on prior art to establish the scientific premise that a single residue mutation is not conclusively indicative of development of resistance to HIV therapy.

As presented and characterized by the examiner, the cited art teach that the variable nature of the observed amino acid substitutions precludes the identification of simple, invariant diagnostic rules for HIV resistance, no preferred order of appearances of any particular substitution is evident, and that the emergence of phenotypic resistance correlated with the appearance of substitutions at various numbers of amino acid residues among at least 11 sites in HIV protease (rather than just one site as addressed in the amended claim).

PREDICTABILITY OF THE ART/BREADTH OF THE CLAIMS

Although the examiner makes bare assertions that the claims are broad in scope, he fails to provide evidence that their breadth is beyond the level of skill in the art.

Kits which detected single mutations already existed in the market and were indicative of resistance to antiviral therapy as of the filing date of the application. *See* "Line Probe Assay For Rapid Detection Of Drug-Selected Mutations In the Human Immunodeficiency Virus Type 1 Reverse Transcriptase Gene," Stuyver L. *et al.*, 1997, *Antimicrob Agents Chemother.* 41:284-91 (attached as Exhibit A).

Other mutations, such as K103N (which was not claimed at the time of invention), were found, which, as single mutations, to confer resistance to all NNRTIs. See Table A, in "Guidance for Industry: Premarket Notifications [510(k) for Vitro HIV Drug Resistance Genotype Assays: Special Controls, U.S. Food and Drug Administration, August 2001 (this publication is attached as Exhibit B; the entire report, and in particular, Table A).

Thus, the examiner, under an incorrect premise, infers that the detection of a single mutation in HIV protease, such as 88T, is not sufficient to reach the objective of the method without undue experimentation.

The examiner fails to provide any evidence demonstrating unpredictability as to whether the claimed method of evaluating the effectiveness of an antiviral therapy of an HIV-infected patient will demonstrate some measurable level. Moreover, it is improper for the examiner to require any showing regarding the degree of effectiveness of therapeutic inventions, such as those now claimed M.P.E.P. § 2107.02; *In re Sichert*, 566 F.2d 1154 (C.C.P.A. 1977).

In addition, applicants enclose a printout of a query performed at Stanford University as the "Stanford HIV Drug Resistance Database", http://hivdb/stanford.edu/cgi-bin/PR_Phenotype.cgi. (a reference in HIV mutations and resistance) where mutation 88T confers resistance to amprenavir (APV), indinavir (IDV), ritonavir (RTV), saquinavir (SQV), lopinavir (LPV), and nelfinavir (NFV), *i.e.*, all PIs which were available at the time of filing of the invention (attached as Exhibit C; file name "88T-Phenotype").

At the time of the invention, the combinations enclosed in claim 7 were sufficient and complete to establish the effectiveness of the different HIV drug regimens available.

AMOUNT OF GUIDANCE PRESENTED/THE PRESENCE OR ABSENCE OF WORKING EXAMPLES

Here, too, the examiner presents a bare allegation without any supporting evidence. The examiner acknowledges that applicants have provided sufficient guidance relating to how to evaluate effectiveness of an antiviral therapy by a particular protease inhibitor, nelfinavir, yet asserts that applicants should have provided evidence for evaluating effectiveness of the therapy with other antiviral drugs by detecting a single mutation at 88T accomplished the desired result of the claimed invention.

There is no evidence of record, however, demonstrating that those skilled in the art would, in fact, have considered such information to have been "necessary" to practice the claimed inventions. Absent some evidence indicating that those skilled in the art, having read applicant's specification, would not be able to practice the claimed inventions, there is no reason to believe that the guidance provided in the specification is insufficient within the meaning of §112.

Thus, as is evident from the foregoing analysis, the examiner's unsupported contentions as to alleged difficulties that those skilled in the art would encounter in practicing the claimed inventions simply do not constitute evidence or technical reasoning of the sort required to substantiate allegations that there is a lack of enablement.

The examiner appears to express concern that "[E]ven though one mutation might contribute to resistance to a drug, detecting just one mutation is not sufficient for successful evaluation of effectiveness of drug therapy". The examiner stated that he remained unpersuaded that detecting a single mutation in HIV protease, such as 88T, would be sufficient to reach the objective of the method without undue experimentation. Claim 7 is not only directed to single mutations pinpointing resistance, but also to a combination thereof, a mutational profile. For example, mutation combinations which produce resistance to PIs and are claimed according to claim 7 are: (I) 88T; (II) 33F and 90M; (III) 88T and 33F; and IV) 88T and 90M. At the time of the invention, the combinations enclosed in amended claim 7 were novel, sufficient and complete to establish the effectiveness of the different HIV drug regimens available. In addition, the 88T mutation indeed confers resistance to all protease inhibitors, not only to nelfinavir.

The examiner, however, fails to provide any evidence that the specification would be insufficient for those skilled in the art to practice the claimed inventions. The examiner further noted that Table 1 in the specification demonstrates that resistance to different antiviral drugs is correlated not with one, but with different mutations and that that the specification does not include examples any other drugs for which single 88T mutation is shown to contribute to the resistance. In addition, the examiner stated that the 88T mutation is related to resistance to a protease inhibitor (PI); however no particular PI is identified.

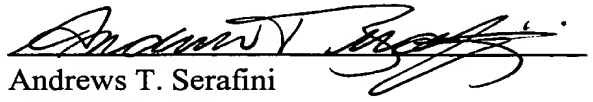
Such examples are not required as a condition for patentability. In fact, it is well-established that an applicant need not include any working examples demonstrating a claimed invention. *In re Fouche*, 169 U.S.P.Q. 429, 434 (C.C.P.A. 1971).

The examiner relies on the preclusion of "invariant diagnostic rules for HIV resistance". Applicants believe the examiner's position is incorrect, seeing the evolution of the HIV resistance profile and the discovery of more HIV antivirals since the filing of applicants' invention. The examiner's reasoning that "the variable nature of the observed amino acid substitutions precludes the identification of simple, invariant diagnostic rules for HIV resistance", is in error, in view of the fact that when observing the invention after the passing of time, the virus resistance profile has evolved and new antivirals have come to the market, influencing as well in the evolution of the HIV resistance profile.

In summary, applicants submit that the examiner has mischaracterized the state of the art and the relative skill of those in the art and has improperly rejected the claims as non-enabled. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, first paragraph, be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: September 27, 2004



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Enclosures:

Exhibit A: "Line Probe Assay For Rapid Detection Of Drug-Selected Mutations In the Human Immunodeficiency Virus Type 1 Reverse Transcriptase Gene," Stuyver L. *et al.*, 1997, *Antimicrob. Agents Chemother.* 41:284-91.

Exhibit B: "Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays: Special Control,

Exhibit C: "Stanford HIV Drug Resistance Database", Stanford University, source: http://hivdb/stanford.edu/cgi-bin/PR_Phenotype.cgi.

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